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APPLICATION NUMBER: *60/529,489*
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RELATED PCT APPLICATION NUMBER: *PCT/US04/42474*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Todd Duncan	Campbell	Petaluma, California

Additional inventors are being named on the One *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

In-situ Formed Alginate Bioreactor with Therapeutic and Cellular Components

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☒ Firm or Individual Name	James F. Hensel				
Address	2911 SW Orchard Hill Place				
Address					
City	Lake Oswego	State	OR	Zip	97035-1194
Country	USA	Telephone	503-244-3232	Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* Cover and 25 Pages

☒ Drawing(s) *Number of Sheets* Three

☐ Application Date Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

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☐ Applicant claims small entity status. See 37 CFR 1.27.

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Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME James F. Hensel

TELEPHONE 503-244-3232

Date December 15, 2003

REGISTRATION NO. *(if appropriate)*

Docket Number:

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INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
James Finley	Hensel	Lake Oswego, Oregon

Number 1 of 1

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 80

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Todd Duncan Campbell
Examiner Name	
Art Unit	
Attorney Docket No.	

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1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80

SUBTOTAL (1) ($) 80

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	James F. Hensel	*Registration No. (Attorney/Agent)*		*Telephone*	503-244-3232
Signature				*Date*	12/15/03

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Endolumen Therapeutics, Inc.
2911 SW Orchard Hill Place
Lake Oswego, OR 97035

December 15, 2003

Commissioner for Patents
Mail Stop Provisional Patent Application
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

Via Express Mail

RE: Provisional Patent Application

Dear Commissioner:

Please find enclosed the following:

Provisional Patent Application Titled "IN-SITU FORMED ALGINATE BIOREACTOR WITH THERAPEUTIC AND CELLULAR COMPONENTS" including:

a. Provisional Application Coversheet (two pages);
b. Fee Transmittal;
c. Specification consisting of a cover page and 25 additional pages;
d. Drawings consisting of three pages; and
e. Check payable to the Commissioner of Patents in the Amount of $80 (claiming small business entity status).

Warm regards,

James F. Hensel

U.S. PROVISIONAL PATENT APPLICATION

IN-SITU FORMED ALGINATE BIOREACTOR WITH THERAPEUTIC AND CELLULAR COMPONENTS

INVENTORS

Name: Todd Duncan Campbell

Name: James Finley Hensel

CORRESPONDENCE:

James F. Hensel

2911 SW Orchard Hill Place

Lake Oswego, OR 97035-1194

IN-SITU FORMED ALGINATE BIOREACTOR WITH THERAPEUTIC AND CELLULAR COMPONENTS

FIELD OF THE INVENTION

The present invention relates generally to endolumen therapeutics, and more specifically to in-situ formed alginate bioreactors with therapeutic and cellular components for delivery of therapeutic agents in a body.

BACKGROUND OF THE INVENTION

Various systems and therapeutic agents continue to be developed for improved long-term delivery of pharmacological and cellular therapeutics. Pills and injections are often ineffective means of administration for long-term treatments because constant drug delivery and higher local concentration are difficult to achieve via these means. Through repeated doses, drugs often cycle through concentration peaks and valleys, resulting in time periods of toxicity and ineffectiveness. In addition, dosages may be dispersed through the human body rather than being directed to a specific area where the treatment is needed.

Local and longer-term delivery of pharmacological and cellular agents at therapeutically effective levels is desirable for a number of medical procedures including those when medical devices are placed permanently within a human body. Drug-eluting coatings or sheaths for vascular stents, for example, are being developed to provide focused, local drug delivery. To increase the effectiveness of inhibitory drugs that are used for angioplasty and stent procedures, a relatively large number of drug molecules may need to be delivered into the intercellular spaces between smooth muscle cells of a vessel so that a therapeutically effective dose of molecules can cross cell membranes. The drug dosage may be difficult to control and direct into the proper intracellular compartments for treatment while minimizing intercellular redistribution of the drug throughout the body via the vascular system.

Long-term in-vivo cellular therapies are also being proposed as an alternative to traditional drug-delivery methods that use oral, intravascular or intramuscular introduction. For medical conditions where a body is unable to produce certain cells or the cells have been damaged, cellular therapeutics may provide long-term therapy. Cellular therapeutics employ living cells that deliver ameliorating natural or engineered biochemicals, or serve as full-scale replacements for defective tissues.

An early example and still widely used complex cellular therapeutics is human bone marrow transplantation as part of a defined treatment regime against leukemia. Since the late 1960s, bone marrow cells have been used to replace the chemotherapy-destroyed marrow of patients afflicted with cancer. These marrow cells can be derived either autologously from the patient before chemotherapy, or from other tissue donors. In some cases, cell therapies involve xenotransplantation of biological implants from completely different species.

A result of non-autologous transplantation is often the lifetime use of immunosuppressive drugs, unless the immune system can be retrained or diverted into accepting the new cells. For example, with pancreatic islet cell transplants, marrow cells from the donor of the islet cells are also transplanted into the host, thereby signaling the host immune system to modify itself and to accept the islet cells.

One proposed approach for eliminating the risk of cells being rejected by the host or the need to use anti-rejection drugs is to encapsulate cells in biocompatible polymeric substances. Intense study in animal models and human clinical trials have recently focused on encapsulating living cells for complex therapeutics, with clinical potential for the treatment of a wide range of diseases.

Cell microencapsulation is a technology where a living cell is infused or implanted in a microcapsule, which protects the cell from the immune system. A microcapsule needs sufficient permeability so that nutrients and oxygen can reach the transplanted cells, and appropriate cellular products, such as insulin from islet cells, can be released into the bloodstream or to adjacent tissues. At the same time, the capsular material should be restrictive enough to exclude immune cells and antibodies that can cause rejection and destroy the implant.

Various types of natural and synthetic polymers, particularly those having a semi-permeable aqueous characteristic, are being explored as encapsulation material. The success of an encapsulation material depends, at least in part, on its stability, chemical definability, lack of toxicity, permeability to oxygen and nutrients as well as the released therapeutic compounds, and its resistance to antibodies or cellular attack.

Materials for potential polymeric encapsulation systems include polysaccharide hydrogels, chitosan, calcium alginate or barium alginate. Photopolymerizable poly(ethylene glycol) (PEG) polymer and polyacrylates such as hydroxyethyl methacrylate methyl methacrylate, also have been proposed encapsulant materials. One encapsulation system employs photolithography techniques to encapsulate living cells in silicon nanocapsules, which have pores of a few nanometers.

A primary purpose for recent research on biocompatible semi-permeable membranes is to create a protective structure around therapeutic cells that grow in vivo and act as a miniature artificial organ or cell factory within the host body. The survival of encapsulated cells requires direct vascularization of the cells along with necessary nutrition and effective protection of the cells from the immune system. In some clinical applications, it is important for a cellular factory to be positioned within close proximity to its target such that the therapy produced by the cells is precisely targeted.

Thus, a desirable cell factory needs to have an immune barrier, while providing for diffusive transport of nutrients to the cell, respiratory byproducts from the surrounding area, and selected compounds to surrounding tissue. The immune barrier properties are required especially for use of non-host derived cell sources or designer deoxyribonucleic acid (DNA) manipulated cells.

Researchers are working to create polymeric materials having drugs, genes or cells incorporated therein for prolonged delivery of biochemical and cellular therapeutics that promote healing, decrease inflammation, manipulate endocrine processes, control cell growth, and provide other therapeutic benefits. Bioabsorbable or biodegradable hydrogels have been designed to release water-soluble therapeutic agents from a matrix formed by a chemical reaction, as described in "Composite Hydrogel Drug Delivery Systems," Sawhney, U.S. Patent No. 6,632,457 granted October 14, 2003. In one

example, biodegradable polymeric matrices encapsulate exogenous genes that are able to diffuse over an extended period of time from nasal or pulmonary areas, as disclosed "Polymeric Gene Delivery System," Mathiowitz et al., U.S. Patent No. 6,620,617 issued September 16, 2003. In another example, polymeric materials, alone or in combination with bioactive agents or cells, are used to treat tissues in endomural areas of solid organs or tubular body structures, some potential materials being described in "Endomural Therapy," Slepian, U.S. Patent Application 2002/0176849 published in November 28, 2002. Biocompatible substances developed for in-situ bioreactors may, for example, include matrices and nucleic acid molecules encoding bioactive agents, as disclosed in "In Situ Bioreactors and Methods of Use Thereof," Pierce et al., U.S. Patent Application No. 2001/0044413 published November 22, 2001.

As an exemplary application of bioreactors and cellular factories, electrical insulating coatings for implanted heart pacemakers and other electrically conductive medical devices may include therapeutic and cellular components such as anti-inflammatory or anti-thrombotic agents, which are produced in vivo for the prolonged use, thereby increasing the effectiveness of the device.

Encapsulated cell therapy systems hold promise for a range of cell-based delivery for long-term therapeutics that treat diabetes, renal failure, hemophilia, cardiovascular diseases, lysomal storage diseases, Huntington's disease, ophthalmic disorders, chronic pain, musculoskeletal diseases, hormonal growth deficiencies, solid tumors, and central nervous system diseases such as amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) and Parkinson's disease. For example, encapsulated cells may enable the directed delivery of highly toxic chemotherapies to cancerous tumors, increasing the options of using chemotherapies, which were previously too toxic, in a localized and localizable fashion. Diabetes is one of the most significant areas of current research for the encapsulation of cells, specifically islet cells of the pancreas that produce insulin. Encapsulated cell therapy is being studied for use in gene therapies such as viral vector designer deoxyribonucleic acid (DNA) from endogenous harvested cells that are vector modified prior to implantation and then implanted.

In cell encapsulation, transplanted cells can be protected from immune rejection by an artificial, semi-permeable membrane such as alginate. Alginate gels have been used in biomedical applications to immobilize living cells or other biomaterials, maintaining good cell viability during long-term culture in the mild environment of the gel network. Conventional pharmaceutical-grade alginate, which is low in endotoxins and other impurities, is extracted from marine brown algae and produced by certain bacteria, for example, Azotobacter vinelandii.

Recently, medical researchers have encapsulated genetically engineered cells and therapeutic cells in immuno-isolating substances to deliver specific substances to targeted treatment areas such a brain tumors. Within tissue-engineering applications, immobilized cells or tissues may be able to serve as bio-artificial organs, while surrounding immuno-isolating substances function as a protection from physical stress and immunological reactions with the host. These cell bioreactors have the potential to excrete biopharmaceuticals and other therapeutic products, and are being clinically tested for the treatment of a variety of diseases like cancer and diabetes. In the case of brain tumors, encapsulated producer cells could be an in-vivo delivery system for specific proteins that target phenotypic features and micro-environmental factors, thereby interfering with tumor growth and differentiation.

In light of the forgoing discussion, targeted and controlled long-term delivery of therapeutic drugs, genes or cells, along with their enscapsulation material still need to be optimized with regard to biocompatibility, mechanical and chemical stability, suitable permeability, immune protection for cellular therapeutics, and the transfer of therapeutic material within the body.

Successful methods and systems for delivery of cellular therapies are able to maintain viable transplanted or implanted cells that produce desirable compounds for extended treatment. Improved long-term delivery systems for therapeutic agents are compliant to surrounding tissues and organs and avoid malapposition of medical devices. Ideally, an encapsulation material and delivery system for various types of pharmacological, gene, and cell therapies eliminate the need for immuno-modulatory

protocols or immunosuppressive drugs, and permit the long-term de novo delivery of therapeutic products to either a localized area or overall life system.

SUMMARY OF THE INVENTION

One aspect of the invention is an alginate bioreactor for treating a mammalian body. The alginate bioreactor includes an alginate matrix and a therapeutic component or a cellular component dispersed within the alginate matrix. A therapeutic agent is eluted from the alginate matrix after the alginate bioreactor is formed within the body.

Another aspect of the invention is a method of treating a medical condition in a mammalian body. An alginate bioreactor including an alginate matrix is formed within a portion of the body. A therapeutic agent is eluted from a therapeutic component or a cellular component dispersed within the alginate bioreactor.

Another aspect of the invention is a system for forming an alginate bioreactor in mammalian body, the system including a first chamber, a second chamber, and an alginate solution injector fluidly coupled to the first chamber and the second chamber. An alginate solution from the first chamber is injected into a portion of the body with an alginate linking agent from the second chamber to form the alginate bioreactor.

BRIEF DESCRIPTION OF THE DRAWINGS

The aforementioned, and other features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims and equivalents thereof. Various embodiments of the present invention are illustrated by the accompanying figures, the figures not necessarily drawn to scale, wherein:

FIG. 1 illustrates an alginate bioreactor for treating a mammalian body, in accordance with one embodiment of the current invention;

FIG. 2 illustrates a system for forming an alginate bioreactor in a mammalian body, in accordance with one embodiment of the current invention; and

FIG. 3 is a flow diagram of a method for treating a medical condition in a portion of a mammalian body, in accordance with one embodiment of the current invention.

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 illustrates an alginate bioreactor **10** for treating a mammalian body **50**, in accordance with one embodiment of the present invention. A cutaway view of an exemplary in-situ formed alginate reactor **10** is shown in the inset. Alginate bioreactor **10** includes an alginate matrix **20** and one or more therapeutic components **30** or cellular components **32** dispersed within alginate matrix **20**. A therapeutic agent **40** is eluted from alginate matrix **20** after alginate bioreactor **10** is formed within body **50**. Alginate matrix **20** of alginate bioreactor **10** may be formed from an alginate solution **60** injected into a portion **52** of body **50** such as a pancreas. Alginate bioreactor **10** may be located in a portion of the body **50** such as a heart, a liver, a pancreas, a kidney, an eyeball, a pericardial space, a cerebral spinal space, a periorganic space, an organ, a vessel, or a tissue.

In one embodiment, the invention provides localized delivery of one or more therapeutic agents **40** from therapeutic components **30** dispersed within alginate bioreactor **10** when alginate bioreactor **10** is formed within body **50** of a mammalian recipient. In another embodiment of the invention, one or more therapeutic agents **40** are delivered long-term from a matrix suitable for maintaining encapsulated cells and aggregates of viable cells from transplanted or implanted cells that produce such therapeutic agents. In yet another embodiment, one or more therapeutic agents **40** are delivered long-term from an alginate matrix **20** that may have one or more therapeutic components **30** and one or more cellular components **32** dispersed therein. When alginate matrix **20** is employed, therapeutic components **30** and cellular components **32** may be uniformly dispersed throughout alginate bioreactor **10**, have a non-uniform profile with a higher concentration of therapeutic components **30** or cellular components **32** nearer the center, or have a non-uniform profile with a higher concentration of therapeutic components **30** and cellular components **32** closer to an outer surface of

alginate bioreactor **10**. In another example, therapeutic components **30** and cellular components **32** agglomerate or collect in regions within alginate bioreactor **10**.

Alginate bioreactor **10** is formed from alginate solution **60** that is injected by an alginate injection system into portion **52** of body **50**. Formed alginate bioreactor **10** includes an alginate matrix **20**. A syringe, an adapter catheter, high-pressure jets, or other injection techniques may be used to inject alginate solution **60** into the desired location in body **50**.

Alginate bioreactor **10** elutes and locally delivers one or more therapeutic agents **40** from therapeutic components **30** and cellular components **32** contained therein to treat medical conditions within body **50**.

Alginate bioreactor **10** provides a mechanism for controlled, time-release characteristics of therapeutic agents **40** from any therapeutic components **30** and cellular components **32** within alginate matrix **20** of alginate bioreactor **10**. Delivery of therapeutic agents **40** may occur over days, weeks, months and even years after formation of alginate bioreactor **10**. With cellular components **32**, therapeutic agents **40** may be continuously produced over the lifetime of the host. In one embodiment, the invention provides localized delivery of one or more therapeutic agents **40** from therapeutic components **30** dispersed within alginate bioreactor **10** when alginate bioreactor **10** is formed within body **50** of the mammalian recipient. In another embodiment, the invention provides long-term delivery of one or more therapeutic agents **40** via alginate matrix **20** that is suitable for maintaining encapsulated cells and aggregates of viable cells from transplanted or implanted cells that produce such therapeutic agents **40**.

In one embodiment, alginate bioreactor **10** includes one or more therapeutic components **30** dispersed within alginate matrix **20**, which controls the elution of therapeutic agent **40** from alginate bioreactor **10**. Therapeutic component **30** includes, for example, an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin

therapy, a lipase, a protein, insulin, bone morphogenetic protein, or a combination thereof. Therapeutic agents **40** released from alginate bioreactor **10** include, for example, therapeutic components **30** themselves or portions thereof.

In another embodiment, one or more cellular components **32** are dispersed within alginate matrix **20** of alginate bioreactor **10** to provide therapeutic agent **40**. Alginate matrix **20** provides an immune barrier for cellular components **32** and controls the elution of therapeutic agents **40** from alginate bioreactor **10**. Cellular component **32** includes, for example, endothelial cells, manipulated cells of designer deoxyribonucleic acid, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, or a combination thereof. Therapeutic components **30** along with cellular components **32** may elute one or more therapeutic agents **40** into surrounding tissue.

Exemplary alginate matrix **20** includes selected therapeutic components **30** and cellular components **32** that produce therapeutic agents **40** for elution from alginate matrix **20** of alginate bioreactor **10**. When cellular components **32** are selected, alginate matrix **20** may serve as an immune barrier so that the immune system of the recipient does not recognize and destroy cellular component **32** contained within alginate matrix **20**, or terminate the production of therapeutic agents **40**. Meanwhile, alginate matrix **20** still allows for the metabolic transfer of nutrients, wastes, and therapeutic proteins and agents to pass through alginate matrix **20** into surrounding body **50**. Therapeutic agents **40** are delivered in close proximity to the treatment site and released from alginate bioreactor **10**. Alginate bioreactor **10** with therapeutic components **30** and cellular components **32** provides long-term expression of the therapeutic agents **40**.

Therapeutic agents **40** from cellular components **32** include, for example, a residue, a byproduct, or natural excretion from the cells. One exemplary therapeutic agent **40** is nitric oxide. Other therapeutic agents **40** from therapeutic components **30** or cellular components **32** include vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid-lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, an

angiogenic agent, an anti-angiogenic agent, an anti-rejection agent, a hormone, a therapeutic component **30**, a cellular component **32**, or a combination thereof.

Alginate bioreactor **10** having therapeutic components **30** or cellular components **32** may help prevent, for example, inflammation or rupture of tissue by eluting of one or more therapeutic agents **40**. For example, eluted therapeutic agents **40** may reduce inflammation in the vicinity of alginate bioreactor **10** and the area of body **50** being treated.

Alginate bioreactor **10** may take the form of an indwelling filter for venous applications that incorporate cellular components **32** and elute therapeutic agents **40** such as streptokinases, kinases or other thrombolytic agents, coumadin materials or other blood thinning agents, nitrous oxide, and other agents.

Living cells or other biomaterials and therapeutic compounds can be immobilized in alginate matrix **20** such as an alginate gel. Cells immobilized in alginate gels maintain good viability during long-term culture, due in part to the mild environment of the gel network. Alginate gel provides a physically protective barrier for immobilized cells and tissue, and inhibits immunological reactions of the host. Alginate matrix **20** provides a location that is viable and productive for cellular components **32**, since alginate matrix **20** allows the diffusion of nutrients to the cell, diffusion of respiratory byproducts to the surrounding area, and diffusion of selected therapeutic components **30** in an unaltered condition from alginate matrix **20**. In some cases, alginate matrix **20** serves as an immune barrier while providing for diffusive transport for therapeutic and cellular materials. The immune barrier properties of alginate matrix **20** are particularly useful for non-host derived cell sources, or manipulated cells of designer deoxyribonucleic acid (DNA). Viral transfection of desirable DNA can occur outside body **50** into cellular components **32** that are encapsulated in situ, reducing the possibility of reaction to the viral vector itself, and allowing for more DNA to be transfected into alginate bioreactor **10**.

One example of a cellular component **32** is endothelial cells that produce nitric oxide, a regulating molecule for smooth muscle cell quiescence and maintenance of vascular smooth muscle cells in the non-proliferative stage. A patient's own endothelial

cells from, for example, microvascular adipose tissue, may be harvested and mixed with alginate solution **60**, and formed along with alginate matrix **20** into alginate bioreactor **10**. Upon implantation, the endothelial cells remain viable and locally produce nitric oxide to regulate and maintain the quiescent nature of smooth muscle cells, which can be a contributor to the production and recruitment of fibroblasts from the media and adventitia of arteries. With the continued long-term production of nitric oxide from the translocated endothelial cells, vascular patency may be maintained for a substantially longer period following bioreactor formation.

Long-term administration of at least one therapeutic agent **40** such as nitric oxide may be provided to portion **52** of body **50** that is diseased or traumatized. For example, disruption of the endothelial lining in a diseased portion of body **50** may result in the reduction of nitric oxide production, leading to the loss of regulation of the smooth muscle cells. Endothelial-derived nitric oxide is a naturally occurring regulation compound that can be produced by, for example, the endothelial cell lining of blood vessels. Endogenously produced nitric oxide molecules can regulate the proliferation of the vascular smooth muscle cells and maintain the cellular quiescence of smooth muscle cells within the vascular architecture. Nitric oxide is also critical to numerous biological processes, including vasodilation, neurotransmission, and macrophage-mediated microorganism and killing of tumors. Nitric oxide may be administrated in a chemically synthesized form as a nitric oxide donor, such as nitroglycerin dispersed within alginate matrix **20**.

Since it is such a small molecule, nitric oxide is able to diffuse rapidly across cell membranes and, depending on the conditions, is able to diffuse distances of more than several hundred microns, as is demonstrated by its regulation of smooth muscle cells, vascular dilation, tissue compliance and physiological tone of the body. Nitric oxide can be produced within alginate matrix **20** and delivered directly to the body. For example, L-arginine, a naturally occurring amino acid, and other nutraceuticals are converted to nitric oxide within alginate matrix **20** by a group of enzymes such as nitric oxide synthases. These enzymes convert L-arginine into citrulline, producing nitric oxide in the

process. In another example, nitric oxide is liberated from diazeniumdiolates, compounds that release nitric oxide into the blood stream and vascular walls.

Alginate bioreactor **10** comprises alginate matrix **20** with, for example, crosslinked chains of mannuronate alginate monomers **62** and guluronate alginate monomers **64**. A predetermined ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64** can be selected and formed into alginate matrix **20** to provide the desired strength, flexibility, and elution rates for therapeutic agents **40**. Alginate, which may be extracted from brown seaweeds such as Phaeophyceae and Laminaria, is a linear copolymer with homopolymeric blocks of mannuronate alginate monomers **62** and guluronate alginate monomers **64**, respectively, covalently linked together in different sequences or blocks.

Alginate matrix **20** may comprise a predetermined ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64**. The alginate monomers can appear in homopolymeric blocks of consecutive guluronate alginate monomers **64**, consecutive mannuronate alginate monomers **62**, alternating mannuronate alginate monomers **62** and guluronate alginate monomers **64**, or randomly organized blocks. The relative amount of each block type varies with the origin of the alginate. Alternating blocks of mannuronate alginate monomers **62** and guluronate alginate monomers **64** form the most flexible chains and are more soluble at lower pH than the other block configurations. Blocks of guluronate alginate monomers **64** form stiffer chain elements, and two guluronate alginate monomeric blocks of more than six monomers each form stable crosslinked junctions with divalent cations such as Ca2+, Ba2+, Sr2+, and Mg2+ leading to a three-dimensional gel network or alginate matrix.

At low pH, protonized alginates form acidic gels. The homopolymeric blocks form the majority of the junctions, and the relative content of guluronate alginate monomers **64** determines the stability of the gel.

Conventional alginate gels can develop and set at temperatures close to that of body **50**. This property of an alginate being able to set at body temperature is particularly useful in applications involving fragile materials like cells or tissue that have a low tolerance for higher temperatures.

Alginate polymers serve as thermally stable cold-setting gelling agents in the presence of divalent cations such as calcium ions from calcium sources. Gelling depends on the ion binding, with the divalent cation addition being important for the production of homogeneous gels, for example, by ionic diffusion or controlled acidification of calcium carbonate. High guluronate alginate monomer content may produce strong, brittle gels with good heat stability, whereas high mannuronate alginate monomer content produces weaker, more elastic gels. At low or very high divalent calcium concentrations, high mannuronate alginates produce stronger gels. When the average chain lengths are not particularly short, the gelling properties correlate with the average guluronate alginate monomer block length having an optimum block size of about twelve monomers, and do not necessarily correlate with the ratio of mannuronate alginate monomers **62** to guluronate alginate monomers **64**, which may be due primarily to alternating mannuronate-guluronate chains. Recombinant epimerases with different specificities may be used to tailor mechanical and transport characteristics of the alginate.

The solubility and water-holding capacity of the alginate depends at least on pH, molecular weight, ionic strength, and the nature of the ions present. Alginate tends to precipitate below a pH of about 3.5. Alginate with lower molecular weight calcium alginate chains of less than 500 monomers shows increasing water binding with increasing size. Lower ionic strength of alginate increases the extended nature of the calcium alginate chains. An alginate gel develops rapidly in the presence of divalent cations like Ca2+, Ba2+, Sr2+, or Mg2+ and acid gels may also develop at low pH. Gelling of the alginate premix occurs when divalent cations take part in the interchain ionic binding between guluronate alginate monomer blocks in the polymer chain, giving rise to a three-dimensional network. Alginates with a high content of guluronate alginate monomer blocks tend to induce stronger gels. Gels made of mannuronate-rich alginate are often softer and more fragile, with a lower porosity, due in part to the lower binding strength between the polymer chains and to the higher flexibilities of the molecules.

The gelling process is highly dependent on diffusion of gelling ions into the polymer network. Methods that may be used for the preparation of alginate gels include dialysis/diffusion and internal gelling.

In the dialysis/diffusion or diffusion-setting method, gelling ions are allowed to diffuse into the alginate solution. This method is commonly used for immobilization of living cells in the alginate gel. Internal gelation, internal setting, or in situ gelling can also help solidify alginate solution **60**. A calcium salt with limited solubility or complexed Ca2+-ions may be mixed into alginate solution **60**, resulting in the release of calcium ions, usually by the generation of acidic pH with a slowly acting acid such as D-glucono-α-lactone. The resultant alginate is a homogenous alginate macrogel. Diffusion setting and internal setting of alginate matrix **20** have different gelling kinetics and result in differences in their gel networks.

FIG. 2 illustrates a system for forming an alginate bioreactor **10** in a portion **52** of a mammalian body, in accordance with one embodiment of the present invention. An alginate bioreactor **10** is being formed within a portion **52** of body **50** such as a kidney. An alginate injection system **70** includes a first chamber **72**, a second chamber **74**, and an alginate solution injector **76**, the latter being fluidly coupled to first chamber **72** and second chamber **74**. An alginate solution **60** from first chamber **72** is injected into portion **52** of the body with an alginate linking agent **68** from second chamber **74** to form alginate bioreactor **10**.

Alginate bioreactor **10** within portion **52** of the body provides directed, localized, time-released delivery of therapeutic agents **40** from therapeutic components **30** and/or cellular components **32** dispersed within alginate bioreactor **10**. In one embodiment, alginate bioreactor **10** with alginate matrix **20** encapsulates and maintains the viability of cellular components **32** and allows the expression of therapeutic agents **40** from the cells to pass through alginate matrix **20** and elute into surrounding targets such as organs, vessels, and other portions of the body.

A ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64** may be selected to provide a predetermined elution characteristic of alginate bioreactor **10**. An alginate premix of mannuronate alginate monomers **62** and guluronate alginate monomers **64**, an alginate solvent **66** such as alcohol or water, and one or more therapeutic components **30** and cellular components **32** are combined to form alginate solution **60** with the determined ratio of mannuronate alginate monomers **62** and

guluronate alginate monomers **64**. Alginate linking agent **68** may be added to alginate solution **60** or maintained separately until combined in the body. When alginate solution **60** and alginate linking agent **68** are injected into the body, the alginate crosslinks, gels, and hardens to form alginate bioreactor **10**. Crosslinking and polymerization of alginate solution **60** may occur in situ while at body temperature, or activated with exposure to ultraviolet light, infrared light, or thermal energy.

Alginate solution injector **76**, such as a single-lumen syringe, may be used to inject the combined or separated alginate solution **60** and alginate linking agent **68** into the body. In cases where alginate solution **60** and alginate linking agent **68** remain separated until injected into the body, a double-lumen syringe may be used for local injection. Alternatively, endoscopic techniques using, for example, guidewires and a bioreactor formation catheter with one or more delivery lumens, inject alginate solution **60** and alginate linking agent **68** endoscopically into the body. Alternatively, a high-pressure injection nozzle or a pair of high-pressure injection nozzles injects alginate solution **60** and alginate linking agent **68** into the body.

FIG. 3 is a flow diagram of a method for treating a medical condition in a portion of a mammalian body, in accordance with one embodiment of the present invention. The method includes various steps to form an alginate bioreactor in the body and to treat one or more medical conditions.

The alginate bioreactor includes an alginate matrix and one or more therapeutic components and cellular components dispersed therein. Formation of the alginate bioreactor may occur in a clinical setting, so that donor-provided cells, for example, may be harvested from a host or donor mammalian body and combined into the alginate solution immediately prior to formation of the alginate bioreactor.

The alginate bioreactor is formed within a portion of the body to provide controlled, time-released delivery of therapeutic agents from therapeutic components and/or cellular components dispersed within the alginate bioreactor. In one embodiment, the alginate bioreactor with an alginate matrix encapsulates and maintains the viability of cellular components, and allows the expression of therapeutic agents from the cells to

pass through the alginate matrix and elute into surrounding targets such as arterial tissues, vessels, organs, and periorganic spaces.

Desired therapeutic components and cellular components are selected along with the desired quantity, as seen at block **80**. Selectable therapeutic components include, for example, an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, a protein, insulin, bone morphogenetic protein, or a combination thereof. Selectable cellular components include, for example, endothelial cells, designer-DNA manipulated cells, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, and combinations thereof. The dose and constituency of added therapeutic and cellular components may be selected based on the desired treatment of the body and the desired elution rate of the therapeutic agents.

A ratio of mannuronate alginate monomers and guluronate alginate monomers may be determined to provide a predetermined elution characteristic of the alginate bioreactor, based on the desired elution characteristics of the therapeutic and cellular components. For example, the block length of mannuronate alginate monomers and the block length of guluronate alginate monomers are selected to achieve suitable strength and flexibility of the bioreactor, while providing controlled delivery of therapeutic and cellular components dispersed within the alginate matrix.

Prior to injection and formation of the alginate bioreactor, the alginate premix, monomers or polymers may be sterilized by passage through a selection of submicron filters, by exposure to radiation in the form of ionizing gamma or electron beams, or by other known methods of rendering a viscous solution sterile. The premix may be mixed in a suitable solvent prior to filtration and then dried, for example, by dialysis or spray drying.

An alginate solution including an alginate premix and an alginate solvent is mixed prior to forming the alginate bioreactor, as seen at block **82**. In one example, the mannuronate alginate monomers, guluronate alginate monomers, and an alginate solvent such as alcohol or water are mixed to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers. The concentration and viscosity of the alginate solution may be reduced with the addition of aqueous cellular or therapeutic components. In another example, the mannuronate alginate monomers, guluronate alginate monomers, alginate solvent, and the selected therapeutic or cellular components are combined to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers. For example, endothelial cells are mixed into a formulation of alginate with appropriate mannuronate and guluronate components into an alginate solution, and the alginate solution used to form the alginate bioreactor. In another example, an alginate premix of mannuronate alginate monomers and guluronate alginate monomers, an alginate solvent such as alcohol or water, and one or more therapeutic components and cellular components are combined to form the alginate solution.

In an optional step, one or more viable cell components may be harvested from the host or a donor mammalian body and mixed into the alginate solution prior to formation of the alginate bioreactor in the body, as seen at block **84**. The cellular component may be genetically manipulated prior to forming the alginate bioreactor. The harvested cells may be further cultured to increase their numbers or further filtered to obtain the desired quantity, quality and type of cells. The harvested viable cellular component, such as endogenous endothelial cells, is mixed into the alginate solution prior to injecting the alginate solution. In another example, freeze-dried cells are mixed into the alginate solution with, for example, an alcohol-based alginate solvent. The freeze-dried cells are reconstituted after the alginate bioreactor is formed within the body. In another example, cells from either a host or donor source are preserved with trehalose and freeze-dried, rendering the cells functional yet in a dehydrated state. Use of cells in a preserved fashion allows for mixing the alginate solution with the cells in advance or conjointly with the medical procedure. One skilled in the art can identify alternative cell-

producing components that can be substituted for endothelial cells and provide therapeutic products from the alginate matrix.

An alginate linking agent is provided, and the alginate solution and the alginate linking agent are injected into a portion of the body with an alginate injection system, as seen at block **86**. The alginate bioreactor is formed by injecting an alginate solution and an alginate linking agent into the portion of the body, and hardening the alginate solution to form the alginate bioreactor. The added alginate linking agent comprises, for example, divalent calcium, divalent barium, divalent strontium, divalent magnesium, a divalent cation, or a source of calcium such as a calcium salt.

In one example, the alginate linking agent is added to the alginate solution immediately prior to injecting the alginate solution into the portion of the body, due to rapid gelling and setting of the alginate matrix. In another example, the alginate linking agent is added to the alginate solution after injecting the alginate solution into the portion of the body. In another example, the alginate linking agent is co-injected into a portion of the body to form the bioreactor. In another example, the alginate linking agent is deposited in the portion of the body prior to injecting the alginate solution. In another example, the alginate linking agent is injected into the body and combined with alginate solution injected from a separate source. In another example, the alginate linking agent is deposited, applied, diffused, or otherwise transferred to the portion of the body prior to injecting the alginate solution. As the alginate solution is injected, the alginate solution coagulates within the portion of the body to form the alginate bioreactor.

The alginate solution is injected into a portion of the body, where the alginate solution crosslinks, gels, and hardens to form the alginate bioreactor. The alginate bioreactor includes an alginate matrix and one or more therapeutic and cellular components. The amount of alginate solution injected into the body is related to the size, quantity and density of the formed bioreactor.

In one example, the alginate solution is injected into the portion of the body with a syringe having at least one lumen. In another example, alginate solution is injected through a bioreactor formation catheter into a sidewall of a vessel, heart, or other endoscopically accessible portion of the body. The bioreactor formation catheter is

positioned, for example, by advancing the distal end of the bioreactor formation catheter over a catheter guidewire to a treatment site in the vessel, a medical procedure as is known in the art. In another example, the alginate solution is injected into the portion of the body with a high-pressure jet.

Once the alginate bioreactor is formed, one or more therapeutic agents may be eluted from therapeutic or cellular components that are dispersed within the alginate bioreactor, as seen at block **88**. Exemplary eluted therapeutic agents from an alginate biorector having therapeutic or cellular components include vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, an angiogenic agent, an anti-angiogenic agent, an anti-rejection agent, a hormone, a therapeutic component, a cellular component, and a combination thereof. In one example, the eluted therapeutic agent comprises nitric oxide from entrained endothelial cells to regulate the proliferation of smooth muscle cells in the body near the formed alginate bioreactor. In another example, the cellular component is reconstituted in the alginate bioreactor, and the therapeutic agent is released from the reconstituted cellular component.

When a cellular component is employed, an alginate bioreactor is formed by a cellularized alginate solution at a location in the body where the cellular component is able to produce and elute a therapeutic agent while reconstituting itself for continued production of the agent. The immune barrier of the alginate matrix protects the cellular components while the alginate bioreactor controls the elution of the therapeutic agent from therapeutic and cellular components within the matrix.

While the embodiments of the invention disclosed herein are presently considered to be preferred, various changes and modifications can be made without departing from the spirit and scope of the invention. The scope of the invention is indicated in the appended claims, and all changes that come within the meaning and range of equivalents are intended to be embraced therein.

CLAIMS

What is claimed is:

1. An alginate bioreactor for treating a mammalian body, the alginate bioreactor comprising:

an alginate matrix; and

one of a therapeutic component or a cellular component dispersed within the alginate matrix, wherein a therapeutic agent is eluted from the alginate matrix after the alginate bioreactor is formed within the body.

2. The alginate bioreactor of claim 1, wherein the alginate matrix of the alginate bioreactor is formed from an alginate solution injected into a portion of the body.

3. The alginate bioreactor of claim 1, wherein the alginate bioreactor is formed in a portion of the body, the portion of the body selected from the group consisting of a heart, a liver, a pancreas, a kidney, an eyeball, a pericardial space, a cerebral spinal space, a periorganic space, an organ, a vessel, and a tissue.

4. The alginate bioreactor of claim 1, wherein the alginate matrix comprises a predetermined ratio of mannuronate alginate monomers and guluronate alginate monomers.

5. The alginate bioreactor of claim 1, wherein the alginate matrix controls the elution of the therapeutic agent from the alginate bioreactor.

6. The alginate bioreactor of claim 1, wherein the therapeutic component is selected from the group consisting of an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-

arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, a protein, insulin, bone morphogenetic protein, and a combination thereof.

7. The alginate bioreactor of claim 1, wherein the cellular component is selected from the group consisting of endothelial cells, manipulated cells of designer deoxyribonucleic acid, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, and a combination thereof.

8. The alginate bioreactor of claim 1, wherein the eluted therapeutic agent comprises nitric oxide.

9. The alginate bioreactor of claim 1, wherein the eluted therapeutic agent is selected from the group consisting of vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, an angiogenic agent, an anti-angiogenic agent, an anti-rejection agent, a hormone, a therapeutic component, a cellular component, and a combination thereof.

10. A method of treating a medical condition in a mammalian body, the method comprising:

forming an alginate bioreactor within a portion of the body, the alginate bioreactor including an alginate matrix; and

eluting a therapeutic agent from one of a therapeutic component or a cellular component dispersed within the alginate bioreactor.

11. The method of claim 10, wherein forming the alginate bioreactor comprises injecting an alginate solution and an alginate linking agent into the portion of the body, and hardening the alginate solution to form the alginate bioreactor.

12. The method of claim 10, wherein the alginate bioreactor controls the elution of the therapeutic agent.

13. The method of claim 10, wherein the eluted therapeutic agent comprises nitric oxide.

14. The method of claim 10, wherein the eluted therapeutic agent is selected from the group consisting of vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, an angiogenic agent, an anti-angiogenic agent, an anti-rejection agent, a hormone, therapeutic component, cellular component, and a combination thereof.

15. The method of claim 10 further comprising:

mixing an alginate solution including an alginate premix and an alginate solvent;

providing an alginate linking agent;

injecting the alginate solution and the alginate linking agent into a portion of the body with an alginate injection system; and

hardening the alginate solution to form the alginate bioreactor.

16. The method of claim 15, wherein the alginate linking agent is added to the alginate solution prior to injecting the alginate solution into the portion of the body.

17. The method of claim 15, wherein the alginate linking agent is added to the alginate solution after injecting the alginate solution into the portion of the body.

18. The method of claim 15, wherein the alginate linking agent is deposited in the portion of the body prior to injecting the alginate solution.

19. The method of claim 15, wherein the added alginate linking agent comprises one of divalent calcium, divalent barium, divalent strontium, divalent magnesium, or a divalent cation.

20. The method of claim 15, wherein the alginate solution is injected into the portion of the body with a syringe having at least one lumen.

21. The method of claim 15, wherein the alginate solution is injected into the portion of the body with a bioreactor formation catheter.

22. The method of claim 15, wherein the alginate solution is injected into the portion of the body with a high-pressure jet.

23. The method of claim 15 further comprising:

determining a ratio of mannuronate alginate monomers and guluronate alginate monomers to provide a predetermined elution characteristic of the alginate bioreactor; and

combining mannuronate alginate monomers, guluronate alginate monomers, the alginate solvent, and the therapeutic component or the cellular component to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers.

24. The method of claim 15 further comprising:

harvesting a viable cellular component from one of a host or a donor; and

mixing the harvested viable cellular component into the alginate solution prior to injecting the alginate solution.

25. The method of claim 24, wherein the harvested viable cellular component comprises endogenous endothelial cells.

26. The method of claim 10 further comprising:

reconstituting the cellular component in the alginate bioreactor, wherein the eluted therapeutic agent is released from the reconstituted cellular component.

27. The method of claim 10 further comprising:

genetically manipulating the cellular component prior to forming the alginate bioreactor.

28. A system for forming an alginate bioreactor in a mammalian body, the system comprising:

a first chamber;

a second chamber; and

an alginate solution injector fluidly coupled to the first chamber and the second chamber, wherein an alginate solution from the first chamber is injected into a portion of the body with an alginate linking agent from the second chamber to form the alginate bioreactor.

29. The system of claim 28, wherein the alginate solution injector is selected from the group consisting of a single-lumen syringe, a double-lumen syringe, a bioreactor formation catheter, a high-pressure injection nozzle, and a pair of high-pressure injection nozzles.

ABSTRACT OF THE DISCLOSURE

The invention provides an alginate bioreactor for treating a mammalian body. The alginate bioreactor includes an alginate matrix, and one or a therapeutic component or a cellular component dispersed within the alginate matrix. A therapeutic agent is eluted from the alginate matrix after the alginate bioreactor is formed within the body. A method for treating a medical condition and a system for forming an alginate bioreactor in a mammalian body are also disclosed.

FIG. 1

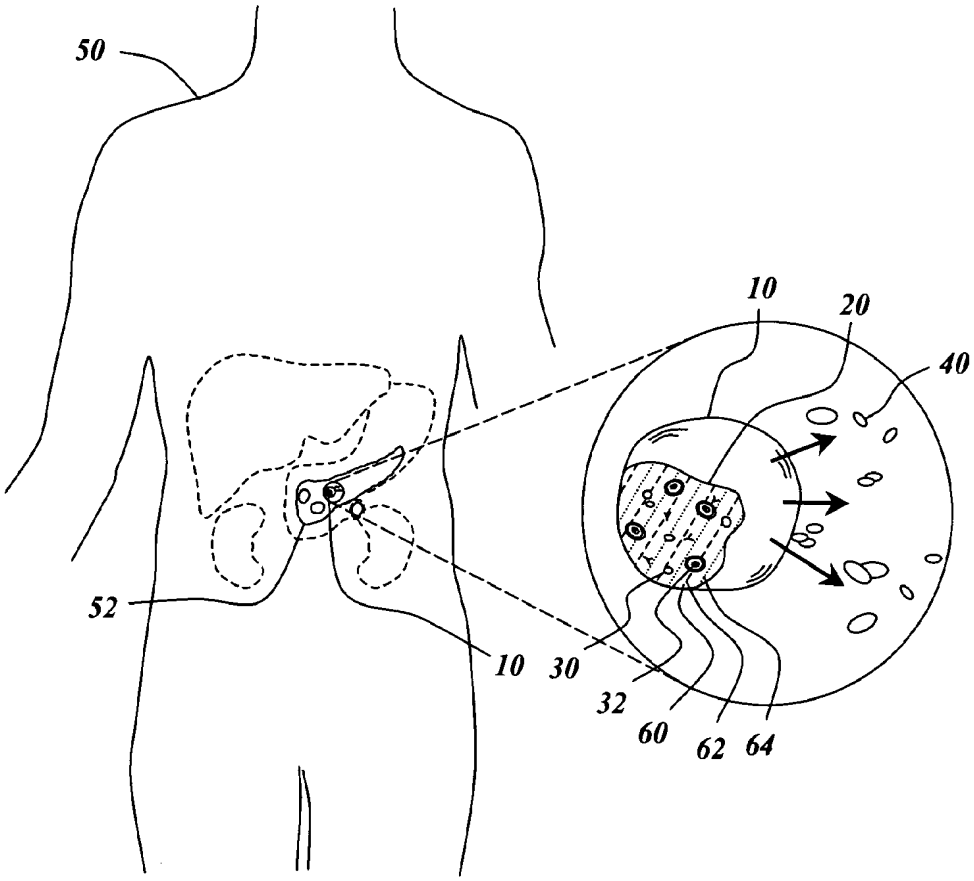


FIG. 2

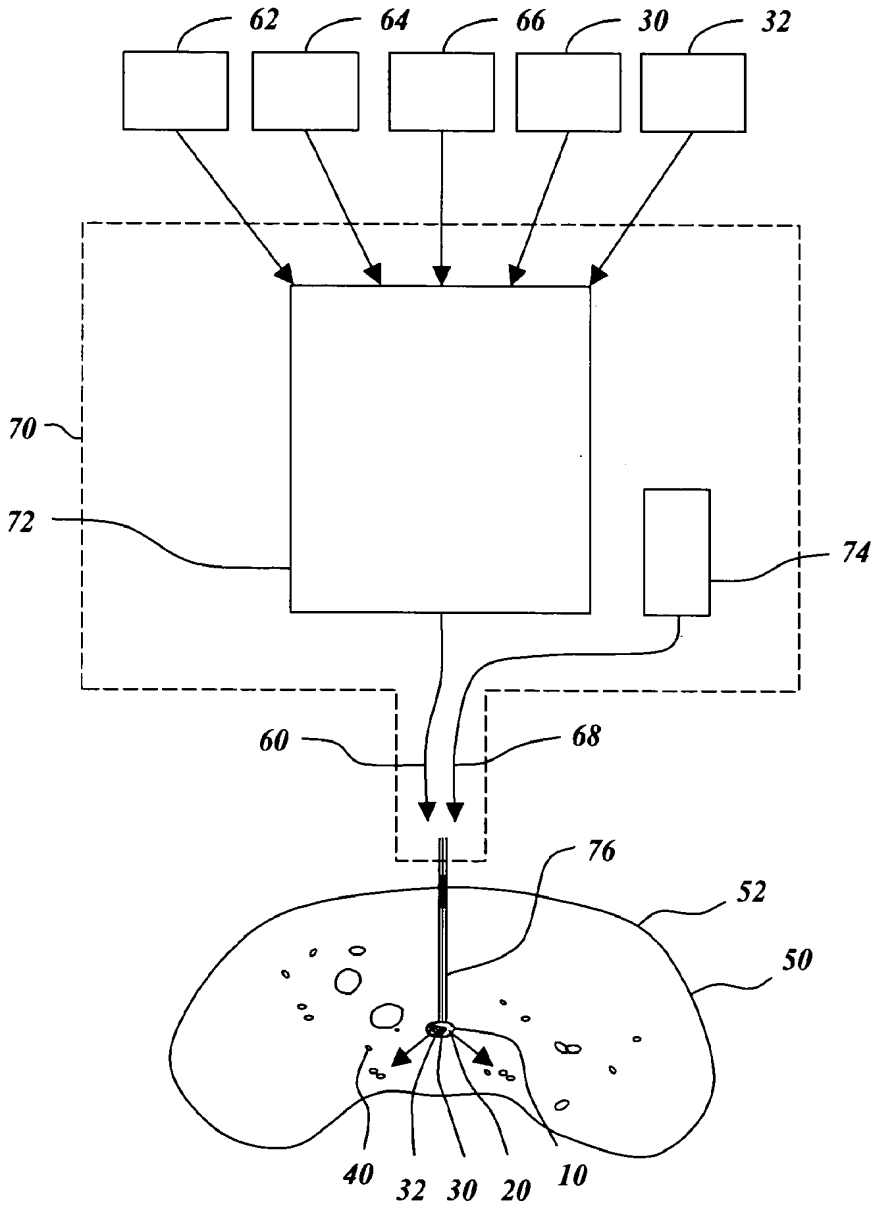
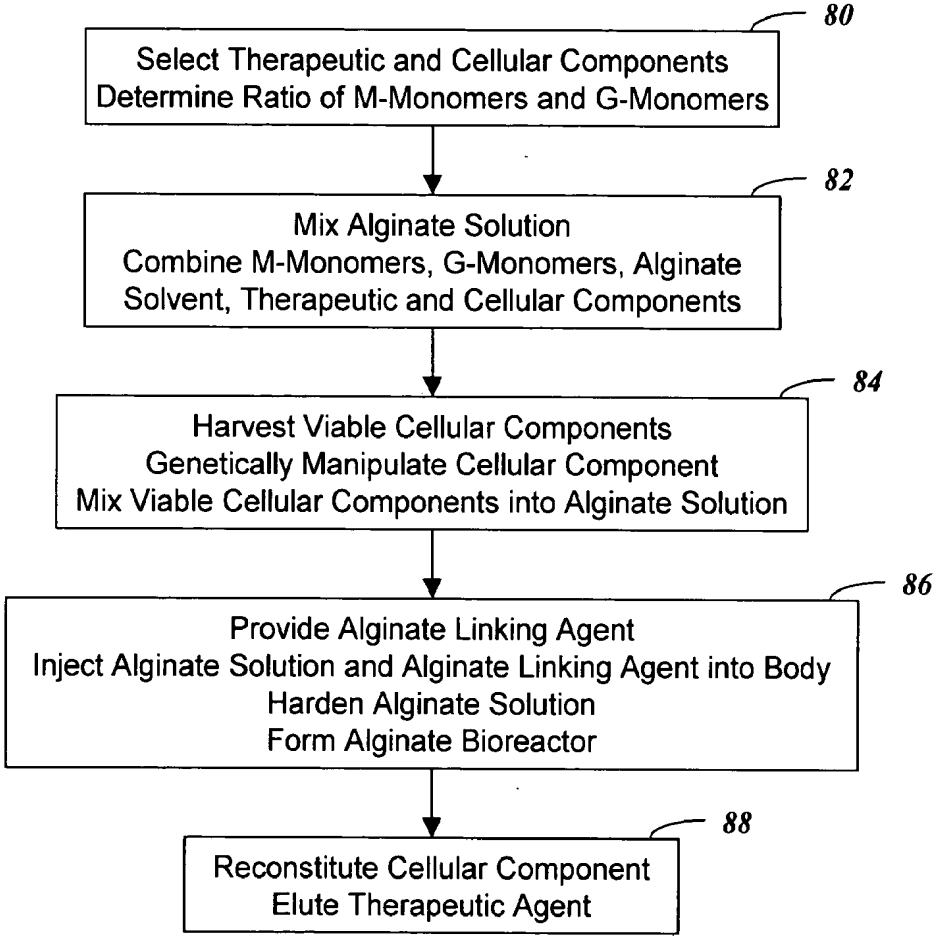


FIG. 3


80
Select Therapeutic and Cellular Components
Determine Ratio of M-Monomers and G-Monomers
82
Mix Alginate Solution
Combine M-Monomers, G-Monomers, Alginate
Solvent, Therapeutic and Cellular Components
84
Harvest Viable Cellular Components
Genetically Manipulate Cellular Component
Mix Viable Cellular Components into Alginate Solution
86
Provide Alginate Linking Agent
Inject Alginate Solution and Alginate Linking Agent into Body
Harden Alginate Solution
Form Alginate Bioreactor
88
Reconstitute Cellular Component
Elute Therapeutic Agent